27. (Twice Amended) The pharmaceutical composition for application to the mucosa according to claim 1 or 3, wherein said mucosa is nasal mucosa.

28. (Twice Amended) The pharmaceutical composition for application to the mucosa according to claim 3, wherein said hemostatic agent is one or more selected from the group consisting of tranexamic acid, epsilon aminocaproic acid, carbazochrome, carbazochrome sulfonate, carbazochrome sodium sulfonate, phytonadione, etamsylate, monoethanol amine oleate, thrombin, hemocoaglase, and adrenochrome monoaminoguanidine mesilate.

a9 amend.

29. (Twice Amended) The pharmaceutical composition for application to the mucosa according to claim 3, wherein the agent other than said hemostatic agent is one or more selected from the group consisting of an antiallergic agent, an antihistamic agent, an anticholinergic agent, a steroid, a vaccine, and a substance for gene therapy, and the mucosa is nasal mucosa.

IN THE SPECIFICATION:

The specification is changed as follows:

Page 1, first paragraph

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a10

The present invention relates to a pharmaceutical composition for application to the mucosa to be used in drug therapy comprising a water-insoluble and/or low water soluble substance, a medicament, and an aqueous medium, and having an osmotic pressure of less than 290 mOsm. More specifically, the present invention relates to a pharmaceutical composition for application to the mucosa comprising a water-insoluble and/or low water soluble substance, a

A10 cancel

medicament, and an aqueous medium, and having an osmotic pressure of less than 290 mOsm, that is superior to conventional pharmaceutical compositions for application to the mucosa, due to efficient and high permeability to the blood at the mucosa.

Page 4, third paragraph

After intensive studies to attain the above first object, the present inventors have found that it is possible to provide a pharmaceutical preparation for application to the mucosa that is superior over conventional liquid composition due to efficient and high permeability through the mucosa to the blood, by formulating a drug that contains a water-insoluble and/or low water soluble substance and that has an osmotic pressure of less than 290 mOsm, and thereby have reached the present invention.

A11

Page 4, fourth paragraph

An enhanced absorption of a drug through the mucosa by controlling the osmotic pressure of a pharmaceutical preparation is disclosed in a patent to Ohwaki and has been reported in a paper by Awazu et al. (Pharm. Res. Vol. 10, No. 9, 1372—1377, 1993). However, these phenomena are only observed in aqueous solution preparations that do not contain a water-insoluble and/or low water soluble substance, and thereby are essentially different from the pharmaceutical preparation of the present invention in which the inclusion of a water- insoluble and/or low water soluble substance is essential. Furthermore, it has been shown in Osada's

Page 5, second paragraph

The patent application by Saunders (WO 92-14473) and Helzner (WO 97-01337) described above describe pharmaceutical preparations containing a water-insoluble and/or low water soluble substance. However, Saunders' patent application (WO 92-11473) makes no description of osmotic pressure of pharmaceutical preparations in general, in its claim, and merely describes in the specification that isotonicity is preferred, and Helzner's patent application makes no description of osmotic pressure of pharmaceutical preparations in general, and merely describes in the specification that the addition of an isotonic agent is preferred. From these patents, therefore, one cannot expect a drastic enhancement in the absorption at low osmotic pressures.

a12

Page 5, second paragraph into page 6

It is surprising therefore that the effect of enhancing drug absorption through the mucosa is drastic when a water-insoluble or low water soluble substance is coexistent. That is, although there are reports that the effect of low osmotic pressure is observed in some aqueous solution preparations, we have found, surprisingly, that the effect can be observed by adding a water-insoluble or low water soluble substance and the effect does not depend on the type of the drug used.

Page 6, first paragraph

Thus, in the first aspect, the present invention 5 provides an aqueous pharmaceutical composition for application to the mucosa comprising one or more water-insoluble substance

a12 cancel

and/or low water soluble substance and one or more medicament, and having an osmotic pressure of less than 290 mOsm. The composition is a pharmaceutical composition for application to the mucosa that is superior over conventional pharmaceutical compositions for application to the mucosa, due to markedly efficient and high permeability to the blood at the mucosa.

Page 6, third paragraph

Thus, in the second aspect, the present invention 25 provides a pharmaceutical composition for application to the mucosa comprising one or more hemostatic agent and one or more medicament, and more specifically, an aqueous pharmaceutical composition for application to the mucosa comprising one or more hemostatic agent, one or more water-insoluble substance and/or low water soluble substance and one or more medicament, and having an osmotic pressure of less than 290 mOsm. The composition is a pharmaceutical composition for application to the mucosa, that is superior over conventional pharmaceutical compositions for application to the mucosa, due to markedly efficient and high permeability and retentivity at the mucosa.

a13

Page 8, second paragraph into page 9

In the first aspect of the present invention, the water-insoluble and/or low water soluble substance is an essential component, and in the second aspect of the present invention, the composition preferably contains a water-insoluble and/or low water soluble substance. Such a water-insoluble or low water soluble substance may be any substance, and preferred examples

a14

include celluloses and more preferably crystalline celluloses. The concentration of the water-insoluble and/or low water soluble substance, that is present as solid particles in an aqueous medium in the first aspect of the present invention, is preferably 0.1% w/w or greater relative to the total amount of the preparation, and more preferably 1% to 10% w/w. The concentration of the water-insoluble and/or low water soluble substance that is present as solid particles in an aqueous medium in the second aspect of the present invention is preferably 0.1% w/w or greater relative to the total amount of the preparation, and more preferably 1% to 10% w/w.

a14 corrected.

Page 9, first paragraph

In any of the aspects of the present invention, preferably the water-insoluble or low water soluble substance that is present as solid particles in an aqueous medium is homogeneously dispersed in the aqueous medium.

Page 21, first paragraph

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twice as high as that of the pharmaceutical preparation having 290 mOsm or greater (Composition Nos. 11 to 13). It has been also shown that even when isotonic at low osmotic pressure, salts such as sodium chloride (Composition Nos. 2 to 4) have higher bioavailability than water—soluble salts such as glucose (Composition Nos. 5 to 7). Furthermore, it indicates that up to about 1.5%, the higher the concentration of the water-insoluble or low water soluble substances is, the higher the bioavailability is (comparison between Composition Nos. 8 and 9 and Composition No.1). Even for the pharmaceutical preparations having a low osmotic pressure, plasma levels were almost equal to the pharmaceutical preparations having isotonic or

a15

high osmotic pressure when they do not contain water-insoluble or low water soluble substances (Composition Nos. 14 to 16). These results indicate that the effect of osmotic pressure of the pharmaceutical preparation which is isotonic or lower on the permeability of the low water soluble substance to the blood at the mucosa is markedly exhibited only when a water-insoluble or low water soluble substance is included, and thereby the effect of the aqueous pharmaceutical composition of the present invention for application to the mucosa was demonstrated.

Page 21, second paragraph into page 22

A15 cont.

When the model drug is a water-soluble low molecular weight substance, 5-carboxy fluorescein, plasma levels of 5-carboxy fluorescein in rabbits that were sprayed with a pharmaceutical preparation having a low osmotic pressure of 6 mOsm (Composition No. 17) to the nasal mucosa were markedly higher than those in rabbits that were sprayed with a pharmaceutical preparation having an almost isotonic osmotic pressure of 340 mOsm (Composition Nos. 19) or with a pharmaceutical preparation having a high osmotic pressure of 4000 mOsm (Composition No. 20), and, as shown in Table 3, the bioavailability is increased by 9 to 17 fold. Furthermore, even for the pharmaceutical preparations having a low osmotic pressure, plasma levels were almost equal to the pharmaceutical preparations having isotonic or high osmotic pressure when they do not contain a water-insoluble or low water soluble substance (Composition Nos. 21 to 22).

Page 22, first paragraph

These results indicate that the effect of osmotic pressure of the pharmaceutical

preparation which is isotonic or lower on the permeability of the low water soluble substance to the blood at the mucosa is markedly exhibited only when a water-insoluble or low water soluble substance is included, and thereby the effect of the aqueous pharmaceutical composition of the present invention for application to the mucosa was demonstrated.

Page 22, third paragraph

Even for the pharmaceutical preparations having a low osmotic pressure, plasma levels were almost equal to the pharmaceutical preparations having isotonic or high osmotic pressure when they do not contain a water-insoluble or low water soluble substance (Composition Nos. 27 and 28).

Page 22, fourth paragraph into page 23

These results indicate that the effect of osmotic pressure of the pharmaceutical preparation which is isotonic or lower on the permeability of the low water soluble substance to the blood at the mucosa is markedly exhibited only when a water-insoluble or low water soluble substance is included, and thereby the effect of the aqueous pharmaceutical composition of the present invention for application to the mucosa was demonstrated.

Page 23, first paragraph

With regard to the result that compares the absorptivity of fluorescein in Example 1 and Comparative example 1, the relationship between the osmotic pressure and bioavailability is shown in Figure 1. Also, with regard to the result that compares the absorptivity of 5-carboxy

fluorescein in Example 2 and Comparative example 2, the relationship between the osmotic pressure and bioavailability is shown in Figure 2. Also, with regard to the result that compares the absorptivity of salmon calcitonin in Example 3 and Comparative example 3, the relationship between the osmotic pressure and bioavailability is shown in Figure 3. It is apparent that in any of the drugs, bioavailability increases with decreased osmotic pressure and that a water-insoluble and/or low water soluble substance represented by crystalline cellulose carmellose sodium is required to obtain a high bioavailability.